

EXHIBIT B

**IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION**

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	Master File No. 2:12-MD-02327 MDL 2327
	JOSEPH R. GOODWIN U.S. DISTRICT JUDGE

**GENERAL REPORT OF
PETER JEPPSON, MD, FACOG, FACS**

I. Background and Qualifications

I graduated from Saint Louis University School of Medicine in Saint Louis, Missouri in 2006, and then completed my residency in Obstetrics and Gynecology at the Cleveland Clinic and Case Western Reserve University MetroHealth Medical Center in Cleveland, Ohio in 2010. Following this I completed additional fellowship training to acquire advanced expertise in Female Pelvic Medicine and Reconstructive Pelvic Surgery, colloquially called Urogynecology, at the Warren Alpert Medical School of Brown University, which I completed in 2013. I passed written and oral examinations for General Obstetrics & Gynecology and Female Pelvic Medicine & Reconstructive Surgery on my first attempt. I am subsequently board-certified by the American Board of Obstetrics and Gynecology, in both Obstetrics and Gynecology and sub-specialty certified in Female Pelvic Medicine and Reconstructive Surgery. In addition, I am a fellow of the American College of Obstetrics and Gynecology and a fellow of the American College of Surgeons. I am currently an Assistant Professor and Director of the Division of Urogynecology at University of New Mexico. I have published over 40 peer-reviewed manuscripts including systematic reviews on urinary incontinence and pelvic organ prolapse. My qualifications, experience, and publications are further detailed in my curriculum vitae, which is provided with this report.

All of my opinions, and the basis of those opinions, are true and correct to the best of my knowledge and belief, including those related to scientific and medical issues, which I believe are true and correct to a reasonable degree of scientific and medical certainty. In addition, my opinions are consistent with published statements by the American Urogynecologic Society (AUGS), Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU), Society of Gynecologic Surgeons (SGS), the American College of Obstetricians and Gynecologists (ACOG), International Continence Society (ICS), and the American Urological Association (AUA).¹ I do, however, reserve the right to supplement this report and my opinions in light of any additional material or information provided to me, including any reports submitted and/or any other discovery that is taken in this case.

I trained at premier FPMRS institutions for both residency and fellowship. This allowed me to learn and become proficient in all non-surgical and surgical treatment modalities for SUI. From a surgical perspective, I am well-versed/proficient/competent in all possible treatment options. Since completing fellowship in 2013, I have been extensively involved in teaching residents and fellows at the University of New Mexico. In addition, I have given grand rounds and taught SUI surgical treatments at local, national, and international meetings. Additional details regarding that experience is set forth in my CV. In addition, I have taught the fellows at the University of New Mexico how to perform these surgeries.

I am being compensated at the rate of \$450 per hour for my preparation of this report. I have testified as an expert witness in one deposition in the last four years, in the Silva v. Ethicon matter on 10/8/2018.

¹ AUGS, SUFU, AUA, ICS, SGS, and ACOG, Groups Reaffirm Position on Use of Vaginal Mesh for Surgical Treatment of Stress Urinary Incontinence (Aug. 16, 2016).

II. Stress Urinary Incontinence

Urinary incontinence is defined as the involuntary loss of urine.² The incidence of urinary incontinence increases with age from approximately 25% of reproductive-aged women to 75% of older women.³ Urinary incontinence can be categorized into several subtypes depending on the underlying cause, the most common types include stress, urgency, and mixed. Treatments vary based on the underlying incontinence type, so it is important to understand the mechanism of the incontinence to be treated since mis-treatment or inadequate treatment will not result in adequate patient improvement. This report will focus on stress urinary incontinence. Stress urinary incontinence is the involuntary leakage of urine that occurs with activities that require effort or exertion.⁴ Stress urinary incontinence is caused by the inability of the urethra to prevent urine leakage during activities that increase intraabdominal pressure, such as coughing, laughing, sneezing, or exercise. A variety of risk factors have been associated with stress urinary incontinence including age, pregnancy, vaginal delivery, pelvic floor trauma, menopause, hysterectomy, obesity, chronic cough, and constipation.⁵

A qualitative review evaluating the impact of SUI found that SUI severely impacts both on quality of life and activities of daily living. In descending order, 62% of patients reported adverse effect on interests and hobbies, 49% on vacation plans, 45% on social life, and 40% on family life.⁶ SUI during exercise has been estimated to occur in 14–49% of women and 12% report avoiding exercise because of stress urinary incontinence.⁷ To put the statistics in context, many women with SUI are uncomfortable or unable to play with their children, participate in activities such as hiking, biking, or swimming because of the fear of incontinence.

Stress urinary incontinence causes significant anxiety and depression, the severity of which is directly proportional to the severity of SUI. That is to say, the more severe the SUI, the greater the anxiety and depression a woman may experience.⁸ Interestingly, although SUI has such a significant impact on women's daily lives, only 25% of affected women seek care. This

² Abrams P, et al., The standardisation of terminology of lower urinary tract function: Report from the Standardisation Sub-committee of the International Continence Society. *Urology* 2003;61:37–49.

³ Abrams P, et al., The standardisation of terminology of lower urinary tract function: Report from the Standardisation Sub-committee of the International Continence Society. *Urology* 2003;61:37–49.

⁴ Abrams P, et al., The standardisation of terminology of lower urinary tract function: Report from the Standardisation Sub-committee of the International Continence Society. *Urology* 2003;61:37–49.

⁵ Shamliyan T, et al., Prevention of urinary and fecal incontinence in adults. *Evid Rep Technol Assess (Full Rep)*. 2007 Dec(161):1-379. PMID: 18457475.

⁶ Black NA and Bowling A. Impact of surgery for stress incontinence on the social lives of women. *Br J Obstet Gynaecol* 1998;105(6):605–12.

⁷ Nygaard I, et al., Is urinary incontinence a barrier to exercise in women? *Obstet Gynecol* 2005;106(2):307–314. *Int Urogynecol J*. 2016 Aug;27(8):1175-84. doi: 10.1007/s00192-016-2954-3. Epub 2016 Feb 10; McKenzie S, et al., Stress urinary incontinence is highly prevalent in recreationally active women attending gyms or exercise classes. *Int Urogynecol J*. 2016 Aug;27(8):1175-84.

⁸ Black NA and Bowling A, Impact of surgery for stress incontinence on the social lives of women. *Br J Obstet Gynaecol* 1998;105(6):605–12; Margalith I, et al., Urinary incontinence in women under 65: quality of life, stress related to incontinence and patterns of seeking health care. *Qual Life Res*. 2004 Oct;13(8):1381-90.

may be partly due to patient embarrassment in discussing the issue with their physician. Unfortunately, less than half of the women that actually seek care receive treatment.⁹

Aside from the quality of life issues already discussed, untreated incontinence is associated with 1.5 to 2.3 times greater risk for falls, which lead to increased overall morbidity, mortality, and health care costs.¹⁰ This is in addition to the financial costs of incontinence resulting from the need to purchase pads/diapers, bed pads, laundry, dry cleaning, and skin care products.¹¹

62% of women that had surgery for SUI reported that SUI caused considerable problems before surgery.¹²

In addition, SUI has repeatedly been shown to adversely affect female sexual function.¹³ The prevalence of sexual dysfunction among women with stress urinary incontinence is approximately 50%. Because of this, it is not surprising that urinary incontinence has been correlated with less frequent sexual activity, desire, and dyspareunia. Reasons for decreased sexual activity include embarrassment, depression, incontinence during sexual activity, marital discord, night-time wetness and need for separate beds. Based on a systematic review, 5% to 38% of women with urinary incontinence completely avoid sexual activity.

III. Non-Surgical Treatment Options for SUI

SUI is amenable to non-surgical and surgical interventions. I have recently published a systematic review on the non-surgical treatments for Urinary Incontinence.¹⁴ Non-surgical interventions aim to strengthen the pelvic floor, modify behaviors that influence bladder function, or employ pharmacological agents that augment urethral sphincter function.

Based on the categorizations used in that systematic review, non-surgical and non-pharmacological SUI treatments for women can be separated into seven main categories

⁹ Minassian VA, et al., The iceberg of health care utilization in women with urinary incontinence. *Int Urogynecol J*. 2012;23(8):1087-1093. Lim R, et al., Effect of Stress Urinary Incontinence on the Sexual Function of Couples and the Quality of Life of Patients. *J Urol*. 2016 Jul;196(1):153-8..

¹⁰ Gibson W, et al., The association between lower urinary tract symptoms and falls: forming a theoretical model for a research agenda. *Neurourol Urodyn*. 2018 Jan;37(1):501-09.

¹¹ Tennstedt SL, et al., Quality of life in women with stress urinary incontinence. *Int Uroyn J Pelvic Floor dysfunct* 2007;18(5):543-9; Subak LL, et al., High costs of urinary incontinence among women electing surgery to treat stress incontinence. *Obstet Gynecol* 2008;111:899-907.

¹² Black NA, Bowling A. Impact of surgery for stress incontinence on the social lives of women. *Br J Obstet Gynaecol* 1998;105(6):605-12.

¹³ Durlade ER and Rowen TS, Urinary Incontinence and Associated Female Sexual Dysfunction. *Sex Med Rev*. 2017 Oct;5(4):470-85.

¹⁴ Balk EM, et al., Pharmacological and Non-Pharmacological Treatments for Urinary Incontinence in Women: A Systematic Review and Network Meta-Analysis of Clinical Outcomes. *Annals of Internal Med*. E-publication planned 3/19/2019; Balk EM, et al., Nonsurgical Treatments for Urinary Incontinence in Women: A Systematic Review Update [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2018 Aug. Report No.: 18-EGC016-EF. AHRQ Comparative Effectiveness Reviews.

including: 1) pelvic floor muscle training (PFMT, to strengthen the pelvic musculature), 2) behavioral training (e.g., bladder training, to teach one to gradually hold urine for longer periods), 3) vaginal cones (to strengthen the pelvic floor muscles and relieve urgency sensation), 4) bladder supports (including pessaries, to support the bladder or urethra and relieve urgency sensation), 5) neuromodulation (including electrical and magnetic stimulation, which may strengthen musculature or to enhance neural control of the bladder), 6) urethral bulking (to improve urethral coaptation (closure) by adding structure to the periurethral tissue), and 7) medications including hormone therapy (such as estrogen), or alpha agonists (such as duloxetine).¹⁵ In addition to those treatment interventions, no treatment is an option. Supportive products such as absorbent pads can be used to lessen the impact during daily activities but pads or diapers do not address the underlying cause of leakage.

We found that most non-pharmacological and pharmacological interventions demonstrated improved symptoms as compared to no treatment.¹⁶ It is important to note that there are no FDA-approved medications for SUI treatment.¹⁷ Duloxetine is approved for use in Europe but is considered off-label use for the treatment of SUI in the U.S.

Although non-surgical treatments improve symptoms, many women seek complete continence, which leads 13% of women to seek surgery for SUI at some point in their life.¹⁸ A randomized controlled trial conducted in the Netherlands demonstrated that midurethral sling surgery resulted in higher subjective and objective cure at one year compared to physiotherapy.¹⁹ As I will discuss in more detail in next section, midurethral slings are considered the gold standard surgical treatment for women that elect to proceed with surgery.²⁰

IV. Surgical Treatment Options for SUI

Over the years, more than 100 surgical procedures have been described in attempt to cure SUI. For the sake of brevity, rather than provide a historical treatise on all possible treatment options, I will focus on the most common treatment options. I will use the AUA guidelines for the treatment of SUI as a guide for which surgeries to discuss. The AUA guidelines recommend consideration be given to four surgical options 1) periurethral bulking agents, 2) synthetic midurethral slings, 3) autologous fascia pubovaginal sling, or 4) Burch colposuspension. I will briefly discuss each in turn.

¹⁵ Balk EM, et al., Pharmacological and Non-Pharmacological Treatments for Urinary Incontinence in Women: A Systematic Review and Network Meta-Analysis of Clinical Outcomes. *Annals of Internal Med.* E-publication planned 3/19/2019.

¹⁶ Balk EM, et al., Pharmacological and Non-Pharmacological Treatments for Urinary Incontinence in Women: A Systematic Review and Network Meta-Analysis of Clinical Outcomes. *Annals of Internal Med.* E-publication planned 3/19/2019.

¹⁷ Lukacz ES, et al., Urinary Incontinence in Women: A Review. *JAMA.* 2017 Oct 24;318(16):1592-1604.

¹⁸ Wu JM, et al., Lifetime risk of stress urinary incontinence or pelvic organ prolapse surgery. *Obstet Gynecol* 2014;123(6):1201-6.

¹⁹ Labrie J, et al., Surgery versus physiotherapy for stress urinary incontinence. *N Engl J Med.* 2013 Sep 19;369(12):1124-33.

²⁰ AUGS, SUFU, AUA, ICS, SGS, and ACOG, Groups Reaffirm Position on Use of Vaginal Mesh for Surgical Treatment of Stress Urinary Incontinence (Aug. 16, 2016).

First, periurethral bulking agents. Several bulking agents have been described in the medical literature. Currently only two options are commercially available. The utility of periurethral bulking is limited in clinical practice because it more of a temporizing measure, not a cure. In the systematic review that I co-authored, we did not find that periurethral bulking agents demonstrated any benefit over no treatment.²¹ The AUA guidelines report “the Panel believes that bulking agents are viable treatments for SUI; however, little long-term data exist for them. Retreatment tends to be the norm for bulking agent therapy and there are inadequate data to allow the recommendation of one injectable agent over another”.²² I agree with the AUA statement, but based on the data and the guidelines periurethral bulking should not be the main stay treatment for such a common condition.

Second, synthetic midurethral slings. These will be discussed in significant detail in the ensuing sections of this report.

Third, autologous fascia pubovaginal slings utilize the patients’ own tissue, typically harvested from the lower abdomen or lateral thigh. This can also be performed using cadaveric allografts or xenografts. The tissue is placed at the bladder neck to prevent SUI. A landmark study published in the NEJM compared pubovaginal slings to the Burch procedure.²³ Pubovaginal slings provided better cure at the expense of more voiding dysfunction.

Fourth, Burch colposuspension. This procedure can be performed through a slightly larger “open” incision, or several small laparoscopic incisions. This is performed by surgically entering the retropubic space. Stitches are then placed at the level of the proximal urethra and then sutured to a ligament that travels along the top of the pubic bone. A laparoscopic Burch was directly compared to a midurethral sling surgery in a randomized-controlled trial, which demonstrated that patients that had a midurethral sling placed had higher success at 1 and 2 years.²⁴

V. The TVT, TVT-O, and TVT-Abbrevio Devices

The TVT device was developed by Ulmsten and colleagues, who started working with Ethicon in 1995 on what ultimately became the TVT device.²⁵ The initial work on the retropubic midurethral sling by Ulmsten and colleagues began much earlier than that and was started based on a belief that traditional surgical treatment options for female SUI were too invasive and the results too unpredictable.²⁶ The midurethral sling was different than prior sling procedures

²¹ Balk EM, et al., Pharmacological and Non-Pharmacological Treatments for Urinary Incontinence in Women: A Systematic Review and Network Meta-Analysis of Clinical Outcomes. *Annals of Internal Med.* E-publication planned 3/19/2019.

²² Kobashi KC, et al., Surgical Treatment of Female Stress Urinary Incontinence: AUA/SUFU Guideline 2017. *J Urol.* 2017 Oct;198(4):875-83.

²³ Albo ME, et al., Burch Colposuspension versus Fascial Sling to Reduce Urinary Stress Incontinence. *N Engl J Med.* 2007;356(21):2143-2155.

²⁴ Trabuco EC, et al., Two-Year Results of Burch Compared With Midurethral Sling With Sacrocolpopexy: A Randomized Controlled Trial. *Obstet Gynecol.* 2018 Jan;131(1):31-38.

²⁵ The history of TVT. *ETH.MESH.03932912-14.*

²⁶ Nilsson Podcast Transcript. *ETH.MESH.01228079-84.*

because the support was provided at the midurethral rather than the bladder neck.²⁷ Ulmsten and colleagues initial studies were encouraging, demonstrating short operative times, excellent efficacy, and no tape rejection.²⁸ They tried multiple different mesh materials before selecting polypropylene, finding it was universally accepted.²⁹

The TVT device is a sterile, single-use device that is 1.1 cm x 45 cm piece of Type 1 Prolene polypropylene, knitted, monofilament mesh that is covered by a plastic sheath and held between two stainless steel trochars that are bonded to the mesh. The device also comes with a TVT introducer that is non-sterile and reusable, and a TVT Rigid Catheter Guide—a non-sterile reusable instrument that facilitates identification of the urethra and bladder neck during the surgical implantation of the TVT mesh.

The TVT-Obturator (“TVT-O”) device is also a 1.1 cm x 45 cm piece of Type 1 Prolene polypropylene, knitted, monofilament mesh that is covered by a plastic sheath. The mesh is attached to plastic tube receptacles that accept the TVT Helical Passers—two stainless steel, curved wire passers that deliver the TVT-O device. The TVT-O also comes with a TVT Atraumatic Winged Guide—a stainless steel accessory instrument that facilitates the passage of the Helical Passers through the dissection tract. The TVT-O device was developed by Dr. Jean de Leval and was based on a modification of an earlier transobturator sling procedure developed by Delorme.³⁰ Dr. de Leval reported on this technique in 2003, describing his novel “inside-out” transobturator midurethral sling technique.³¹ Ethicon launched the TVT-O device in early 2004.³² Ethicon’s positive experience with the TVT device—which, again, utilized the same Prolene mesh and also was positioned under the midurethra—also supported the feasibility of the TVT-O device. The TVT device rapidly became one of the most popular surgical procedures to treat SUI.³³

The TVT-Abbrevio device is a 1.1 cm x 12 cm piece of Type 1 Prolene polypropylene, knitted, monofilament mesh that is covered by a plastic sheath. Like the TVT-O, the mesh is covered by sheaths and held between two Helical Passer Sheaths (white polyethylene tube receptacles). The sheaths are bonded to the mesh and include Positioning Lines made of Prolene monofilament suture material. The TVT-Abbrevio mesh includes a Placement Loop that aids in symmetric positioning of the mesh graft. It also includes two stainless steel curved wire Helical

²⁷ Ulmsten U, et al., An Ambulatory Surgical Procedure Under Local Anesthesia for Treatment of Female Urinary Incontinence. *Int Urogynecol J.* 1996;7:81-6.

²⁸ Ulmsten U, et al., A Multicenter Study of Tension-Free Vaginal Tape (TVT) for Surgical Treatment of Stress Urinary Incontinence. *Int Urogynecol J.* 1998;9:210-13; Nilsson CG, et al., Long-term Results of the Tension-Free Vaginal Tape (TVT) Procedure for Surgical Treatment of Female Stress Urinary Incontinence. *Int Urogynecol J.* 2001 (Suppl2):S5-S8.

²⁹ Petros P, Creating a gold standard surgical device: scientific discoveries leading to TVT and beyond: Ulf Ulmsten Memorial Lecture 2014. *Int Urogynecol J.* 2015 Apr;26(4):471-6.

³⁰ History of TVT-O, ETH.MESH.03932909-11.

³¹ De Leval J, Novel Surgical Technique for the Treatment of Female Stress Urinary Incontinence: Transobturator Vaginal Tape Inside-Out. *Eur Urol* 2003;44:724-30.

³² History of TVT-O, ETH.MESH.03932909-11.

³³ Reisenauer C, et al., Transobturator vaginal tape inside-out – A minimally invasive treatment of stress urinary incontinence: Surgical procedure and anatomical conditions. *Eur J Obstet & Gynecol and Reprod Biol.* 2006;127:123-29.

Passers and an Atraumatic Winged Guide to assist with implantation of the mesh. The TVT-Abbrevio device was developed by Dr. de Leval and Dr. David Waltregny, who modified the existing TVT-O procedure “with the aim of reducing the incidence of postoperative groin pain as well as the rather theoretical risk of obturator nerve injury.”³⁴ Drs. de Leval and Waltregny and colleagues (including Dr. Piet Hinoul of Ethicon) performed an anatomic comparison of the TVT-O and the modified TVT-O procedure in a cadaver study, and found the shorter sling traversed significantly less muscular structures than the traditional TVT-O, while still consistently anchoring in the obturator membrane at a safe distance from the obturator canal.³⁵ De Leval, Waltregny, and Dr. Alexandre Thomas published the results of a prospective randomized trial comparing outcomes in TVT-O and TVT-Abbrevio patients, and found cure rates at one year of follow-up of 91.7% and 90.7%, respectively, for the TVT-O and TVT-Abbrevio slings, with less groin pain and less intense groin pain in the TVT-Abbrevio patients on day 0 and 1, but not thereafter. There were no intra-operative complications. One TVT-O patient required placement of a suprapubic catheter, and a TVT-Abbrevio patient underwent an immediate tape release procedure. Both of those patients were cured of SUI without any urinary retention or de novo urge symptoms at one year. One TVT-O patient had a vaginal mesh exposure requiring partial mesh excision. There were no other reported complications during the follow-up period.³⁶ At three-year follow-up, 85.7% of the TVT-O patients and 87.7% of the TVT-Abbrevio patients had a negative cough test, 1.3% of the TVT-Abbrevio patients and 4.1% of the TVT-O patients reported but did not complain of thigh pain, and all had a pain score of ≤ 3 .³⁷ Multiple subsequent studies support the safety and efficacy of the TVT-Abbrevio device.³⁸

³⁴ Waltregny D and de Leval J, New Surgical Technique for Treatment of Stress Urinary Incontinence—TVT-ABBREVO: From Development to Clinical Experience. *Surg Technol Int.* 2012 Dec;22:149-57.

³⁵ Hinoul P, et al., An anatomic comparison of the traditional TVT-O versus a modified TVT-O procedure. 2010 ICS Abs. 875.

³⁶ De Leval J, et al., The original versus a modified inside-out transobturator procedure: 1-year results of a prospective randomized trial. *Int Urogynecol J* 2011;22:145-156.

³⁷ Waltregny D and de Leval J, New Surgical Technique for Treatment of Stress Urinary Incontinence—TVT-ABBREVO: From Development to Clinical Experience. *Surg Technol Int.* 2012 Dec;22:149-57.

³⁸ Dati S, et al., Single-Incision Minisling (Ajust) vs. Obturator Tension-Free Vaginal Shortened Tape (TVT Abbrevio) in Surgical Management of Female Stress Urinary Incontinence. *Int J Gynecol & Obstet.* 2012;119S3:S70 Poster M432; Kurien A, Narang S, Han HC. TVT Abbrevio Prospective analysis over 22 months in a tertiary care hospital. *Br J Obstet Gynecol.* 2014 Jan;121(2):235–236 EP13.17; Dati S, et al., TVT-Abbrevio: When and why? *Tech Coloproctol* 2013;17:136; Canel V, et al., Postoperative groin pain and success rates following transobturator midurethral sling placement: TVT ABBREVO system versus TVT obturator system. *Int Urogynecol J.* 2015 Oct;26(10):1509-16; Tommaselli GA, et al., Efficacy and safety of the trans-obturator TVT-Abbrevio device in normal weight compared to overweight patients affected by stress urinary incontinence. *Eur J Obstet Gynecol Reprod Biol.* 2016 Feb;197:116-9; Shaw JS, et al., Decreasing transobturator sling groin pain without decreasing efficacy using TVT-Abbrevio. *Int Urogynecol J.* 2015 Sep;26(9):1369-72; Capobianco G, et al., TVT-ABBREVO: efficacy and two years follow-up for the treatment of stress urinary incontinence. *Clin Exp Obstet Gynecol.* 2014;41(4):445-7; Feng S, et al., Three- and twelve-month follow-up outcomes of TVT-EXACT and TVT-ABBREVO for treatment of female stress urinary incontinence: a randomized clinical trial. *World J Urol.* 2018 Mar;36(3):459-65; Sun Y, et al., The Efficiency and Safety of Tension-Free Vaginal Tape (TVT) Abbrevio Procedure Versus TVT Exact in the Normal Weight and Overweight Patients Affected by Stress Urinary Incontinence. *Urology.* 2017 Dec;110:63-69; Riachi L and Provost K, A new minimally invasive treatment option for stress urinary incontinence in women: TVT Abbrevio, a shorter sling with an inside-out transobturator approach. *Surg Technol Int.* 2013 Sep;23:176-80; Kurien A, et al., Tension-free vaginal tape-Abbrevio procedure for female stress urinary incontinence: a prospective analysis over 22 months. *Singapore Med J.* 2017 Jun;58(6):338-342;

Midurethral slings such as the TVT, TVT-O, and TVT-Abbrevio are one of the most significant advances in women's health in the last 20 years. The midurethral sling was FDA-cleared for use in the US in 1998 and has subsequently become the preferred surgical option because it is so effective with low complication rates.³⁹

To quote the AUA position statement, "extensive data exist to support the use of synthetic polypropylene mesh suburethral slings for the treatment of female SUI, with minimal morbidity compared with alternative surgeries. Advantages include shorter operative time/anesthetic need, reduced surgical pain, reduced hospitalization, and reduced voiding dysfunction."⁴⁰ Based on all of these factors, the midurethral sling is, and continues to be the gold-standard treatment for women with SUI.⁴¹

The midurethral sling device is safe and effective, as demonstrated by numerous high-quality randomized controlled trials, systematic reviews and meta-analyses, and position statements by many professional societies.⁴² ACOG says it this way: "There are substantial safety and efficacy data that support the role of synthetic mesh midurethral slings as a primary surgical treatment option for stress urinary incontinence in women." ACOG then quotes AUGS and SUFU stating MUS are the "standard of care" in the surgical treatment of stress urinary incontinence.⁴³ In fact, the TVT is the most-studied surgical device, with data that exceed 15

Utekar T, et al., Studying the newer TVT-O Abbrevio tape in comparison with the standard TVT-O tape for management of stress urinary incontinence. *Eur J Obstet Gynecol Reprod Biol.* 2016;206:e117; Li WL, et al., A comparative study on treating female stress urinary incontinence with TVT-Abbrevio and TVT-Obturator.

³⁹ Jonsson Funk M, et al., Trends in the surgical management of stress urinary incontinence. *Obstet Gynecol* 2012;119(4):845-51.

⁴⁰ AUA Position Statement on the Use of Vaginal Mesh for the Surgical Treatment of Stress Urinary Incontinence (SUI). (Revised Oct. 2018).

⁴¹ AUGS & SUFU Position Statement on Mesh Midurethral Slings for Stress Urinary Incontinence (published Jan. 2014, updated June 2016 and Feb. 2018); Schimpf MO, et al., Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. *AJOG* 2014;211(1):71.e1-71.e27; Ford AA, et al., Mid-urethral sling operations for stress urinary incontinence in women. *Cochrane Database Syst Rev.* 2017;7:CD006375.

⁴² AUGS Position Statement on Mesh Midurethral Slings for Stress Urinary Incontinence 2014 (2018 update); ACOG & AUGS, Urinary Incontinence in Women, Practice Bulletin Summary No. 155, Nov. 2015; IUGA Position Statement on Mid-Urethral Slings for Stress Urinary Incontinence, Jul. 2014; Ogah J, et al., Minimally Invasive Synthetic Suburethral Sling Operations for Stress Urinary Incontinence in Women: A Short Version Cochrane Review. *Neurourol and Urodyn.* 2011;30:284-91; Ford AA, et al., Mid-urethral sling operations for stress urinary incontinence in women. *Cochrane Database Syst Rev.* 2015 Jul 1;(7):CD006375; Tommaselli GA, et al., Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanalysis. *Int Urogynecol J* 2015 Sep;26(9):1253-68; Richter HE, et al., Retropubic versus Transobturator Midurethral Slings for Stress Incontinence. *N Engl J Med* 2010;362;22:2066-76; Schimpf MO, et al., Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. *Am J Obstet Gynecol.* 2014 Jul;211(1):71.e1-71.e27; Cox A, et al., Surgical management of female SUI: is there a gold standard? *Nat. Rev. Urol.* 2013;10:78-89; Laurikainen E, et al., Five-year Results of a Randomized Trial Comparing Retropubic and Transobturator Midurethral Slings for Stress Incontinence. *Eur Urol* 2014 Jun;65(6):1109-14.

⁴³ ACOG Practice Bulletin No. 155: Urinary Incontinence in Women. Committee on Practice Bulletins—Gynecology and the American Urogynecologic Society. *Obstet Gynecol.* 2015 Nov;126(5):e66-81. doi: 10.1097/AOG.0000000000001148; American Urogynecologic Society, Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction. Position Statement on Mesh Midurethral Slings for Stress Urinary Incontinence.

years of follow-up.⁴⁴ Midurethral slings can be placed in a retropubic or transobturator fashion. Success rates for retropubic slings are reported to be between 51 and 88%.⁴⁵

Transobturator midurethral slings were developed to simplify and reduce risks associated with retropubic slings by avoiding the retropubic space.⁴⁶ Multiple studies confirm the efficacy of the transobturator sling with success rates ranging between 43 and 92%.⁴⁷ An extensive body of published data supports the safety and efficacy of the TVT-O device in the intermediate- and long-term.⁴⁸

⁴⁴ Ethicon Tension-Free Midurethral Sling: Market Update, ETH.MESH.10281865; Nilsson CG, et al., Seventeen years follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. *Int Urogynecol J* 2013 Aug; 24(8):1265-9; Serati M, Tension-free Vaginal Tape for the Treatment of Urodynamic Stress Incontinence: Efficacy and Adverse Effects at 10-Year Follow-Up. *Eur Urol* 2012;61:939-946; Laurikainen E, et al., Five-year Results of a Randomized Trial Comparing Retropubic and Transobturator Midurethral Slings for Stress Incontinence. *Eur Urol* 2014 Jun;65(6):1109-14; Aigmueller T, et al., Ten-year follow-up after the tension-free vaginal tape procedure. *Am J Obstet Gynecol* 2011 Nov;205(5):496.e1-5; Heinonen P, et al., Tension-free vaginal tape procedure without preoperative urodynamic examination: long-term outcome. *Int J Urol*. 2012 Nov;19(11):1003-9; Olsson I, et al., Long-term efficacy of the tension-free vaginal tape procedure for the treatment of urinary incontinence: a retrospective follow-up 11.5 years post-operatively. *Int Urogynecol J* 2010 Jun;21(6):679-683; Song PH, et al., The 7-year outcome of the tension-free vaginal tape procedure for treating female stress urinary incontinence. *BJU Int* 2009 Oct;104(8):1113-1117; Liapis A, et al., Long-term efficacy of tension-free vaginal tape in the management of stress urinary incontinence in women: efficacy at 5- and 7-year follow-up. *Int Urogynecol J* 2008 Nov;19(11):1509-1512; Chêne G, et al., Long-term results of tension-free vaginal tape (TVT) for the treatment of female urinary stress incontinence. *Eur J Obstet Gynecol Reprod Biol* 2007 Sep;134(1):87-94; Jelovsek JE, et al, Randomized trial of laparoscopic Burch colposuspension versus tension-free vaginal tape: long-term follow up. *BJOG* 2008 Jan;115(2):219-225; Senningsen R, et al., Long-term follow-up of the retropubic tension-free vaginal tape procedure. *Int Urogynecol J*. 2013 Aug;24(8):1271-8; Prien-Larsen JC, et al., Long-term outcomes of TVT and IVS operations for treatment of female stress urinary incontinence: monofilament vs. multifilament polypropylene tape. *Int Urogynecol J* 2009 Jun;20(6):703-709; Serati M, et al., TVT for the Treatment of Urodynamic Stress Incontinence: Efficacy and Adverse Effects at 13-Year Follow-Up. *Neurourol and Urodynamics DOI* 10.1002/nau; McCracken GR, et al., Five Year Follow-up Comparing Tension-Free Vaginal Tape and Colposuspension, *Ulster Med J* 2007 Sep;76(3):146-149; Jin-Yan Wu JY, et al., Surgical therapies of female stress urinary incontinence: experience in 228 cases, *Int Urogynecol J* 2010 Jun;21(6):645-649; Vesna Bjelic-Radisic V, Patient-related Outcomes and Urinary Continence Five Years After the Tension-Free Vaginal Tape Operation, *Neurourology and Urodynamics* 2011;30(8):1512-1517; Celebi I, et al., Results of the tension-free vaginal tape procedure for treatment of female stress urinary incontinence: a 5 year follow-up. *Arch Gynecol Obstet* 2009 Apr;279(4):463-467.

⁴⁵ Kobashi KC, et al., Surgical Treatment of Female Stress Urinary Incontinence: AUA/SUFU Guideline 2017. *J Urol*. 2017 Oct;198(4):875-83.

⁴⁶ Kobashi KC, et al., Surgical Treatment of Female Stress Urinary Incontinence: AUA/SUFU Guideline 2017. *J Urol*. 2017 Oct;198(4):875-83; De Leval J, Novel Surgical Technique for the Treatment of Female Stress Urinary Incontinence: Transobturator Vaginal Tape Inside-Out. *Eur Urol* 2003;44:724-30.

⁴⁷ Kobashi KC, et al., Surgical Treatment of Female Stress Urinary Incontinence: AUA/SUFU Guideline 2017. *J Urol*. 2017 Oct;198(4):875-83.

⁴⁸ Cheng D, et al., Tension-free vaginal tape-obturator in the treatment of stress urinary incontinence: a prospective study with five-year follow-up. *Eur J Obstet Gynecol Reprod Biol* 2012;161:228-231; Angioli R, et al., Tension-Free Vaginal Tape Versus Transobturator Suburethral Tape: Five-Year Follow-up Results of a Prospective, Randomised Trial. *Eur Urol* 2010;58:671-677; Liapis A, et al., Efficacy of inside-out transobturator vaginal tape (TVTO) at 4 years follow up. 2010;148:199-201; Groutz A, et al., Long-Term Outcome of Transobturator Tension-Free Vaginal Tape: Efficacy and Risk Factors for Surgical Failure. *J of Women's Health* 2011;20(10):1525-1528; Laurikainen E, et al., Five-year Results of a Randomized Trial Comparing Retropubic and Transobturator Midurethral Slings for Stress Incontinence. *Eur Urol* 2014 Jun;65(6):1109-14; Serati M, et al., TVT-O for the

Retropubic and transobturator slings have been compared to each other. Short-term analyses demonstrate equivalence between these options, however, at five years the retropubic slings were noted to have slightly higher success rates.⁴⁹ When compared to pubovaginal fascial slings and Burch colposuspension, the midurethral slings typically have better outcomes and fewer adverse events.⁵⁰

As previously discussed, there are many different potential causes of urinary incontinence. It is common for stress and urgency incontinence to co-exist. When counselling patients regarding efficacy or success, it is important to clearly discuss that treatment of SUI will not fully address patients with mixed urinary incontinence. Even for patients with “pure” SUI, there is also a risk of incomplete or inadequate relief of symptoms. It is important to note this is true for any incontinence surgery. As noted in the AUA/SUFU Guidelines in 2017, “with any intervention there is a risk of continued symptoms of SUI immediately after the procedure or recurrent SUI at a later time that may require further intervention.”⁵¹ Midurethral sling surgery typically leads to a significant improvement in productivity and quality of life.⁵² The vast majority of women that I have cared for clinically are happy they had surgery and tell me they wish they had undergone surgery sooner.

As with any surgery, placement of MUS carries inherent risks. Because MUS surgery is minimally invasive, requiring minimal dissection, implanted through a small vaginal incision, there is decreased potential for wound-healing problems. Nevertheless, all surgical procedures, including those designed to treat incontinence have inherent risks, such as infection or bleeding. Wound infections and urinary tract infections can occur following any incontinence surgery.⁵³ Mesh-related complications do occasionally occur following polypropylene sling placement, but (according to the AUA) these complication rates are “acceptably” low.⁵⁴ Published data

Treatment of Pure Urodynamic Stress Incontinence: Efficacy, Adverse Effects, and Prognostic Factors at 5-Year Follow-up. *Eur Urol* 2013;63:872–78; Athanasiou S, et al., Seven years of objective and subjective outcomes of transobturator (TVT-O) vaginal tape: Why do tapes fail? 2014;25:219–225.)

⁴⁹ Kenton K, et al., 5-year longitudinal followup after retropubic and transobturator mid urethral slings. *J Urol* 2015; 193(1):203-10.

⁵⁰ ACOG Practice Bulletin No. 155: Urinary Incontinence in Women. Committee on Practice Bulletins—Gynecology and the American Urogynecologic Society. *Obstet Gynecol*. 2015 Nov;126(5):e66-81. doi: 10.1097/AOG.0000000000001148; Rehman H, et al., Traditional suburethral sling operations for urinary incontinence in women. *Cochrane Database Syst Rev* 2011 Jan 19;(1):CD001754; Ward K and Hilton P. Prospective multicentre randomised trial of tension-free vaginal tape and colposuspension as primary treatment for stress incontinence. United Kingdom and Ireland Tension-free Vaginal Tape Trial Group. *BMJ* 2002;325:67; Jelovsek JE, et al., Randomised trial of laparoscopic Burch colposuspension versus tension-free vaginal tape: long-term follow up. *BJOG* 2008;115:219–25; discussion 225; Anger JT, et al. Trends in surgical management of stress urinary incontinence among female Medicare beneficiaries. *Urology* 2009;74(2):283–7; Jonsson Funk M, et al., Trends in the surgical management of stress urinary incontinence. *Obstet Gynecol* 2012;119(4):845–51.

⁵¹ Kobashi KC, et al., Surgical Treatment of Female Stress Urinary Incontinence: AUA/SUFU Guideline 2017. *J Urol*. 2017 Oct;198(4):875-83.

⁵² AUGS & SUFU Position Statement on Mesh Midurethral Slings for Stress Urinary Incontinence (published Jan. 2014, updated June 2016 and Feb. 2018); Schimpf MO, et al., Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. *Am J Obstet Gynecol* 2014;211(1):71.e1-71.e27.

⁵³ Schimpf MO, et al., Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. *Am J Obstet Gynecol* 2014;211:71.e1-27.

⁵⁴ AUA Position Statement on the Use of Vaginal Mesh for the Surgical Treatment of Stress Urinary Incontinence (SUI). (Revised Oct. 2018).

demonstrates that severe complications are not common with midurethral slings. Relatively rare complication rates coupled with good results is the reason that the midurethral sling is the most common surgery for SUI. It is worth noting that complications are less with MUS than other similarly effective surgeries such as the pubovaginal sling or the Burch colposuspension.⁵⁵ Specifically, the midurethral sling has less blood loss, operative time, bowel injuries, hematoma formation, wound infections, length of hospital stay, and prolonged urinary retention. In my opinion, the risks associated with the use of the TVT, TVT-O, and TVT-Abbrevio devices are outweighed by the benefits of using the devices. The devices are safe and effective.

Two of the more common complications specifically associated with midurethral sling placement are 1) vaginal mesh exposure (which is often caused by wound separation) and 2) urinary retention. Vaginal mesh exposure is often caused by wound separation and is relatively easy to manage surgically, either with suture closure or partial removal of the mesh. Mesh exposures occur in approximately 2% of patients that get a midurethral slings.⁵⁶ Urinary retention can be caused by a sling that is tensioned too tightly, this can also be treated surgically by a sling release, also a minor surgery. Release of a midurethral sling is needed approximately 1% of the time.⁵⁷ It is important to note that urinary retention can also occur if Burch sutures are tensioned too tightly, or if a fascial sling is tensioned too tightly. The rate of retention lasting longer than six weeks post-operatively after Burch procedures or pubovaginal sling procedures is more than twice as high as it is after transobturator or retropubic sling procedures.⁵⁸

Fortunately, severe complications associated with vaginal mesh, including mesh erosion into the bladder or chronic pain are uncommon. A recent retrospective population-based study from England including a total of 95,057 patients provides long-term safety data for the midurethral sling.⁵⁹ This study reported low rates of sling removal for any indication including mesh exposure, chronic pain, or retention. A sling removal was performed for 1.4% at one year, 2.7% at 5 years, and 3.3% at 9 years.

To be clear, I identify with a statement by AUGS that it is pro-science, not pro-mesh or anti-mesh. And all available evidence supports the midurethral sling as the best treatment option for most women with SUI.⁶⁰ This position is shared by multiple medical societies. In 2016, six medical societies, the AUA, ACOG, ICS, SGS, SUFU, and AUGS issued a joint statement

⁵⁵ Schimpf MO, et al., Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. *Am J Obstet Gynecol* 2014;211(1):71.e1-71.e27; Dmochowski RR, et al., Update of AUA guideline on the surgical management of female stress urinary incontinence. *J Urol* 2010;183(5):1906-14.

⁵⁶ Schimpf MO, et al., Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. *Am J Obstet Gynecol* 2014;211(1):71.e1-71.e27; Ford AA, et al., Mid-urethral sling operations for stress urinary incontinence in women. *Cochrane Database Syst Rev*. 2017;7:CD006375.

⁵⁷ Schimpf MO, et al., Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. *Am J Obstet Gynecol* 2014;211(1):71.e1-71.e27; Ford AA, et al., Mid-urethral sling operations for stress urinary incontinence in women. *Cochrane Database Syst Rev*. 2017;7:CD006375.

⁵⁸ Schimpf MO, et al., Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. *Am J Obstet Gynecol* 2014;211(1):71.e1-71.e27.

⁵⁹ Gurol-Urganci I, et al., Long-term Rate of Mesh Sling Removal Following Midurethral Mesh Sling Insertion Among Women With Stress Urinary Incontinence. *JAMA* 2018 Oct 23;320(16):1659-69.

⁶⁰ AUGS is Neither Pro-Mesh; nor Anti-Mesh – AUGS is Pro-science and Science and Evidence Must Lead the Way (May 16, 2018), available at <https://www.augs.org/augs-is-neither-pro-mesh-nor-anti-mesh---augs-is-pro-science-and-science-and-evidence-must-lead-the-way/>.

representing more than 84,000 urologists, gynecologists and other healthcare professionals reaffirming their collective support of the use of mid-urethral slings, including synthetic polypropylene mesh slings, for the treatment of SUI.⁶¹ They specifically state that “synthetic polypropylene mesh sling placement is the most common surgery performed for SUI and is recognized in clinical practice guidelines as a standard of care for this condition.”⁶²

There is significant utility to the design of the TVT, TVT-O, and TVT-Abbrevio devices. The fact that they are macroporous allows for excellent tissue ingrowth, allows for a tension-free placement, and results in a low infection rates. The fact that they have been well-studied gives me confidence as a surgeon that I know the potential risks and benefits of the devices and can counsel my patients effectively regarding their treatment options. The fact that the devices come sterilized is a positive design attribute, as that also reduces the potential for infection. The fact that the devices are implanted via a small vaginal incision and small incisions on either the suprapubic area or groin crease is a positive design attribute because it makes the devices minimally invasive, reduces the operative time, reduces post-operative pain, reduces recovery time, reduces the likelihood of creating an unsightly scar, and reduces the likelihood of post-operative wound complications such as wound dehiscence or incisional hernias. The utilization of Prolene polypropylene mesh in the devices is desirable because the graft is of a consistent durability, strength, availability, and quality, thereby avoiding the possibility of suboptimal fascial quality with fascial sling procedures. The fact that the devices are made of knitted, monofilament mesh is desirable because monofilament tapes have fewer mesh erosions than multifilament tapes.⁶³

VI. Response to Contentions by Plaintiffs’ Experts

The mesh used in the TVT, TVT-O, and TVT-Abbrevio devices is made of Prolene polypropylene, which has been used in surgeries for decades. This mesh is a large pore Type I macroporous, lightweight mesh, which is known for its biocompatibility.⁶⁴ The pore size of the Prolene mesh in each of the devices is 1.3 mm.⁶⁵ Polypropylene suture has been used for decades in cardiac, general, gynecologic, orthopedic, thoracic, and urologic surgery. Polypropylene mesh was first used in surgery to repair abdominal wall hernia in 1958 and has been used extensively in humans for this purpose for the past 30 years.⁶⁶ A variety of materials

⁶¹ AUGS, SUFU, AUA, ICS, SGS, and ACOG, Groups Reaffirm Position on Use of Vaginal Mesh for Surgical Treatment of Stress Urinary Incontinence (Aug. 16, 2016), available at https://www.sgsonline.org/assets/docs/Special_Reports/jointmeshstatement_final%208%2016%2016.pdf.

⁶² Anger JT, et al. Trends in surgical management of stress urinary incontinence among female Medicare beneficiaries. *Urology* 2009;74(2):283–7; ACOG Practice Bulletin No. 155: Urinary Incontinence in Women. Committee on Practice Bulletins—Gynecology and the American Urogynecologic Society. *Obstet Gynecol.* 2015 Nov;126(5):e66-81. doi: 10.1097/AOG.0000000000001148.

⁶³ Ogah J, et al., Minimally Invasive Synthetic Suburethral Sling Operations for Stress Urinary Incontinence in Women: A Short Version Cochrane Review. *Neurourol and Urodyn.* 2011;30:284-91.

⁶⁴ Ford AA, et al., Mid-urethral sling operations for stress urinary incontinence in women. *Cochrane Database Syst Rev.* 2015 Jul 1;(7):CD006375.

⁶⁵ Moalli PA, et al., Tensile properties of five commonly used mid-urethral slings relative to the TVT. *Int Urogynecol J.* 2008;19:655-63.

⁶⁶ Baylón K, et al., Past, Present and Future of Surgical Meshes: A Review. *Membranes* (Basel). 2017 Aug 22;7(3); Lockhart K, et al., Mesh versus non-mesh for inguinal and femoral hernia repair. *Cochrane Database Syst Rev.* 2018 Sep 13;9:CD011517.

have been tried over time and polypropylene monofilament large pore mesh is commonly accepted around the world as the best material available for midurethral slings.⁶⁷

Some plaintiffs' experts contend that the Prolene polypropylene mesh degrades in vivo, resulting in pain and other complications. I have not seen evidence of this in my practice, and the level 1 clinical evidence pertaining to polypropylene mid-urethral slings does not support this theory. The theory that Prolene polypropylene degrades in vivo is belied by the extensive body of data supporting the efficacy and safety of the devices made of the Prolene polypropylene mesh used in the TVT, TVT-O, and TVT-Abbrevio devices. A recent article by Thames and colleagues found that the cracked layer on the outside of an explanted polypropylene fiber identified as degraded Prolene by some researchers is actually "an adsorbed protein-formaldehyde coating, resulting from the well-established formalin-protein fixation process, which occurs immediately upon placing an explant in formalin."⁶⁸ Similarly, de Tayrac and Letouzey found that the surface cracking on explanted polypropylene mesh was a biofilm that, once removed, revealed no degradation of the polymer.⁶⁹ The Clavé article frequently relied on by plaintiffs' experts as evidence of polypropylene degradation notes that the authors could not confirm their hypotheses regarding polypropylene degradation, including whether or not direct oxidation of the polypropylene occurred in vivo. The authors also only analyzed 1/3 of the explanted specimens that were available to be analyzed.⁷⁰

Likewise, the extensive data supporting the safety and efficacy of mid-urethral slings does not support the theory that the Prolene polypropylene in the slings is cytotoxic or elicits an intense chronic foreign body reaction. Falconer and colleagues demonstrated that the inflammatory response to implantation of Prolene polypropylene was minimal.⁷¹ That is consistent with my own experience using the TVT, TVT-O, and TVT-Abbrevio devices, and with the body of literature discussed in this report including systematic reviews, randomized controlled trials, long-term studies, and registry studies demonstrating low rates of complications—including but not limited to pain—with the use of the devices. Ethicon studied whether the Prolene mesh in the TVT device was cytotoxic, and while it found "some evidence to suggest that the [polypropylene] mesh from the [TVT] may have cytotoxic potential," it concluded that "the cytotoxicity of the [polypropylene] mesh observed in vitro does not translate into any clinical significance or adverse patient outcomes" when factoring in relevant clinical evidence.⁷²

⁶⁷ Ford AA, et al., Mid-urethral sling operations for stress urinary incontinence in women. *Cochrane Database Syst Rev.* 2017;7:CD006375; Schimpf MO, et al., Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. *Am J Obstet Gynecol* 2014;211(1):71.e1-71.e27; AUGS & SUFU Position Statement on Mesh Midurethral Slings for Stress Urinary Incontinence (Jan. 2014).

⁶⁸ Thames SF, et al., The myth: in vivo degradation of polypropylene-based meshes. *Int Urogynecol J.* 2017 Feb;28(2):285-97.

⁶⁹ De Tayrac R and Letouzey V, Basic science and clinical aspects of mesh infection in pelvic floor reconstructive surgery. *Int Urogynecol J.* 2011 Jul;22(7):775-80.

⁷⁰ Clavé A, et al., Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants. *Int Urogynecol J.* 2010;21:261-70.

⁷¹ Falconer C, et al., Influence of Different Sling Materials on Connective Tissue Metabolism in Stress Urinary Incontinent Women. *Int Urogynecol J.* 2001 (Suppl 2):S19-S23.

⁷² T. Barbolt Memo re Cytotoxicity Risk Assessment for the TVT (Ulmsten) Device, Aug. 8, 1997, at 1. ETH.MESH.00349228.

I have not observed any difference in the way laser-cut mesh slings and mechanically cut mesh slings perform. (The TVT and TVT-O devices are available with both laser-cut and mechanically cut mesh, and the TVT-Abbrevio is only available with laser-cut mesh.) Ethicon's benchtop testing showed no physical significant differences between the laser-cut mesh and the mechanically cut mesh within the range of physiologic forces.⁷³ Additionally, the clinical literature pertaining to Ethicon's mid-urethral slings pre-dating the availability of laser-cut mesh in 2006 does not show a difference in terms of complication rates when compared to the clinical literature from 2006 to the present day. A recent study by Rusavy and colleagues showed there was no clinically significant difference between the two types of mesh.⁷⁴

Roping, curling, and fraying of the mesh in the TVT, TVT-O, and TVT-Abbrevio devices does not occur if the devices are implanted per the directions set forth in the IFU. I have not observed any particle loss from the slings that is of any clinical significance, nor does the published literature describe any such clinically significant particle loss.

Both my clinical experience using the TVT, TVT-O, and TVT-Abbrevio and the published literature regarding such slings demonstrates that the devices do not contract or shrink to a clinically significant extent.⁷⁵

The pore size of the mesh in the TVT, TVT-O, and TVT-Abbrevio slings is optimal. It is macroporous and allows for tissue ingrowth, while still allowing for macrophages and leukocytes to transverse the pores, reducing the risk of infection.⁷⁶

There is considerable evidence that polypropylene does not cause cancer. In a large population-based study from Sweden of more than 5 million women, including all (almost 21,000) women that had undergone MUS surgery since 1997, they found that the type 1 polypropylene mesh used in midurethral slings is not associated with increased cancer risk.⁷⁷

VII. Alternative Designs and Procedures

⁷³ Clinical Expert Report re: Laser Cut Mesh. ETH.MESH.01784823-28.

⁷⁴ Rusavy Z, et al., Are the same tapes really the same? Ultrasound study of laser-cut and mechanically cut TVT-O post-operative behavior.

⁷⁵ Nilsson CG, et al., Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. *Int Urogynecol J* 2013 Aug;24(8):1265-1269; Lo T-S, et al., Ultrasound Assessment of Mid-Urethra Tape at Three-Year Follow-Up After Tension-Free Vaginal Tape Procedure. *J Urol* 2004;63(4):671-5; Dietz HP, et al., Does the tension-free vaginal tape stay where you put it? *Am J Obstet Gynecol* 2003;188:950-3; Lukacz ES, et al., The effects of the tension-free vaginal tape on proximal urethral position: a prospective longitudinal evaluation. *Int Urogynecol J*. 2003;14:179-84.

⁷⁶ Amid PK, Classification of biomaterials and their related complications in abdominal wall hernia surgery. *Hernia* 1997;1:15-21.

⁷⁷ Altman D, et al., Cancer Risk After Midurethral Sling Surgery Using Polypropylene Mesh. *Obstet Gynecol* 2018;131(3):469-74; King AB, et al., Is there an association between polypropylene midurethral slings and malignancy? *Urology*. 2014 Oct;84(4):789-92; Linder BJ, et al., Evaluation of the local carcinogenic potential of mesh used in the treatment of female stress urinary incontinence. *Int Urogynecol J*. 2016 Sep;27(9):1333-6.

In my opinion, the TVT, TVT-O, and TVT-Abbrevio devices are as safe as any option for treatment of stress incontinence, and likely safer than more invasive procedures such as an autologous or allograft fascial sling (pubovaginal sling) procedure or Burch procedure. Those procedures can also cause pelvic pain or dyspareunia, and I have seen and removed permanent sutures used in Burch or MMK procedures from the bladder. Additionally, alternative surgical options for SUI can also fail to cure the patient's incontinence. I agree with the American Urogynecologic Society (AUGS) and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) Position Statement: "the polypropylene mesh midurethral sling is the recognized worldwide standard of care for the surgical treatment of stress urinary incontinence. The procedure is safe, effective, and has improved the quality of life for millions of women."⁷⁸ It is pure speculation or conjecture to purport or state that mesh slings with larger pore sizes or lighter-weight mesh than the typical type 1 polypropylene mesh, such as that used in the TVT, TVT-O, and TVT-Abbrevio would have been safer or more effective. The majority of medical literature regarding midurethral slings, including large network studies funded by the NIH (such as the UITN, or PFDN) utilized TVT slings. The mesh in the TVT-O and the TVT-Abbrevio slings is the same mesh as that used in the TVT slings. Published literature regarding lighter-weight and larger pore meshes used in pelvic floor surgeries show that the use of those meshes does not avoid the risks involved with the use of mesh like the Prolene mesh in the TVT; dyspareunia and mesh exposure can still occur.⁷⁹ Ethicon developed a prototype of a transobturator midurethral sling that utilized a partially absorbable mesh similar to the Ultrapro mesh, but found that excessive force was required to remove the sheaths from the mesh during cadaveric testing.⁸⁰ The long-term outcomes of such light weight mesh are not known at this time.

Autologous fascial sling procedures require an additional incision, either on the abdomen or lateral thigh, to harvest the autologous fascia. The harvest site presents additional risk of wound complications and/or hernia formation. A randomized controlled trial by the Urinary Incontinence Treatment Network published in 2007 compared the outcomes for patients undergoing a Burch procedure or autologous fascial sling procedure showed success rates at 24-month follow-up of 49% and 66% respectively. Adverse events in the sling patients included cystotomy, recurrent UTI, pyelonephritis, catheter complication, voiding dysfunction leading to surgical revision, pelvic pain, bleeding, and wound complication requiring surgical intervention. Adverse events following the Burch procedure included ureteral injury, ureterovaginal fistula, incidental vaginotomy, incidental cystotomy, suture erosion into the bladder, recurrent UTI, pyelonephritis, catheter complications, bleeding, and wound complications requiring surgical intervention.⁸¹ The AUA/SUFU Guidelines from 2017 note that "[e]fforts to use other materials, such as porcine dermis and cadaveric fascia, as substitution for the autologous fascia have shown

⁷⁸ Nager C, et al., Position statement on mesh midurethral slings for stress urinary incontinence. *Female Pelvic Med Reconstr Surg* 2014;20(3):123-5.

⁷⁹ Milani AL, et al., Trocar-guided mesh repair of vaginal prolapse using partially absorbable mesh: 1 year outcomes. *Am J Obstet Gynecol* 2011;204:74.e1-8; Quemener J, et al., Rate of re-interventions after transvaginal pelvic organ prolapse repair using partially absorbable mesh: 20 months median follow-up outcomes. *Eur J Obstet Gynecol and Reprod Biol.* 2014;175:194-98.

⁸⁰ Ethicon R&D Memorandum on PA Mesh Assessments for TVTO-PA, 12/12/12. ETH.MESH.09922570-78.

⁸¹ Albo ME, et al., Burch Colposuspension versus Fascial Sling to Reduce Urinary Stress Incontinence. *N Engl J Med.* 2007;356(21):2143-2155.

inferior results.”⁸² Studies show that allograft slings can have high failure rates and the grafts can degrade and become fragmented and attenuated.⁸³ Although very rare, there is the potential for cadaveric grafts to retain donor DNA and antigens or be contaminated with bacteria.⁸⁴ All surgical procedures for the treatment of SUI share the potential for intraoperative or postoperative complications.

VIII. IFU and Other Educational Materials

In my opinion, the TVT, TVT-O, and TVT-Abbrevio IFUs provided appropriate information for surgeons to be able to use the devices safely. They included information regarding the indications for use of the devices, contraindications, and instructions on how to implant the devices. They also contained warnings and potential adverse reactions. The warnings and adverse reactions noted a potential for infection, de novo detrusor instability, injury to large vessels, nerves, bladder, and bowel, extrusion, erosion, fistula formation, and inflammation, and over-correction causing lower urinary tract obstruction. The IFUs for the TVT-O and TVT-Abbrevio also warned of possible transient leg pain lasting 24-48 hours. The “Actions” section of the IFUs notes that Prolene mesh elicits a minimal inflammatory reaction in tissue based on animal studies, and that the reaction is transient and followed by the deposition of a thin fibrous layer of tissue which can grow through the interstices of the mesh, incorporating it into adjacent tissue. Based on my experience implanting hundreds of midurethral slings made of the Prolene TVT mesh (used in the TVT, TVT-O, and TVT-Abbrevio), these are accurate statements. The IFUs also note that the devices should be used only by physicians trained in the surgical treatment of stress urinary incontinence and specifically in implanting the device referenced in the IFU. The IFUs are used by surgeons who have been through—at a minimum—medical school and residency training and bring with them fundamental knowledge of surgical risks associated with any pelvic floor surgery such as a risk that the procedure will fail to cure the condition it was meant to treat, as well as temporary or chronic pain including dyspareunia. Residents are expected to gain an understanding of the indications for use of graft materials in pelvic reconstructive surgery, their characteristics, and potential complications associated with use of the grafts. They are also expected to understand the benefits and risks of the various anti-incontinence procedures.⁸⁵ Fellows seeking advanced training in urogynecology should learn how to perform a variety of evidence-based surgical procedures for SUI and to describe the indications, intra- and post-operative complications and success of a variety of incontinence surgeries, including both mesh and non-mesh surgeries.⁸⁶ In my opinion, the IFU does not need to contain information regarding risks that are not evidence-based, clinically significant or

⁸² Kobashi KC, et al., Surgical Treatment of Female Stress Urinary Incontinence: AUA/SUFU Guideline 2017.

⁸³ Carbone JM, et al., Pubovaginal sling using cadaveric fascia and bone anchors: disappointing early results. J Urol 2001 May;165(5):1605-1611; Soergel TM, et al., Poor Surgical Outcomes after Fascia Lata Allograft Slings, Int Urogynecol J 2001;12:247-253; Fitzgerald MP, et al., Failure of allograft suburethral slings. BJU Int 1999;84:785-788.

⁸⁴ Fitzgerald MP, et al., The antigenicity of fascia lata allografts. BJU Int 2000;86:826-28; Choe JM and Bell T, Genetic material is present in cadaveric dermis and cadaveric fascia lata. J Urol 2001 Jul;166:122-4.

⁸⁵ AUGS, Resident Learning Objectives.

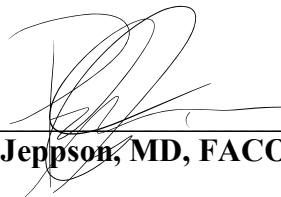
⁸⁶ The American Board of Obstetrics and Gynecology and The American Board of Urology, Guide to Learning in Female Pelvic Medicine and Reconstructive Surgery 2012.

information on risks that are commonly known by gynecologists, urologists, or urogynecologists.⁸⁷

Ethicon also produced the Surgeon's Resource Monograph, which set forth expert opinions on the use of the Gynecare TVT device. The opinions provided in the monograph were distilled from a Gynecare TVT Summit Meeting held in June 2000 at which the experience of more than 20 active proctors was shared. The monograph was prepared "for the purpose of training surgeons in a safe, reproducible, and standard way." The monograph provided information regarding complications of the use of the TVT device, patient selection, anesthesia, and surgical technique. It also included information regarding precautions, adverse reactions, contraindications, and post-operative care. There is no equivalent document that I am aware of that covers the same information for the Burch procedure, fascial sling procedures, or other traditional stress urinary incontinence surgeries.

I agree with the AUA/SUFU guidelines,⁸⁸ which state "prior to selecting synthetic MUS procedures for the surgical treatment of SUI in women, physicians must discuss the specific risks and benefits of mesh as well as the alternatives to a mesh sling" It specifically states "the Panel believes that patients considering surgical intervention should be counseled thoroughly regarding the use of synthetic mesh to treat SUI. The focus should be on the benefits, the potential risks and the FDA (U.S. Food and Drug Administration) safety communication regarding MUS, thereby allowing the patient to make a goal-oriented, informed decision as to how she would like to approach her SUI treatment." This is consistent with what is done in clinical practice. I think that physicians should read through IFUs for products they use but an IFU will never adequately provide all possible information. It is interesting that the AUA guidelines do not even list the IFU as a resource for providers. A recent survey of North American Urologists found that a minority (36.9%) of the survey respondents—79.3% of whom identified as general urologists and 12.7% as FPMRS-trained urologists—who reported placing midurethral slings and/or a mesh prolapse repair kit had read the Instructions for Use.⁸⁹

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⁸⁷ 21 C.F.R. Pt. 801, Sec. 801.109(c).

⁸⁸ Kobashi KC, et al., Surgical Treatment of Female Stress Urinary Incontinence: AUA/SUFU Guideline 2017. J Urol. 2017 Oct;198(4):875-83.

⁸⁹ Kirkpatrick G, et al., Transvaginal Mesh Placement and the Instructions for Use: A Survey of North American Urologists. Urol Prac. 2019 Mar;6:135-39.